wherein X is CH_2, CH-alkyl or $C(alkyl)_2$, R_1 is H, alkyl, C_3-C_7 cycloalkyl or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl or C_3-C_7 cycloalkyl, unsubstituted or substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

D2 cont'd

11. The pharmaceutical composition according to claim 9, wherein the longest chain in R_{11} comprises 5-7 carbon atoms.

12. The pharmaceutical composition according to claim 11, wherein the longest chain in R_{11} comprises 5 carbon atoms.--

REMARKS

Claims 1-5 and 7-12 are pending in the instant application. Claims 1, 8 and 9 are independent. Applicants amended claim 2 to correct typographical errors. The specification on pages 8 and 14 provide support for new claims 8-12. Applicants have not raised any issues of new matter.

Applicants have added 5 new claims that were indicated as being a new issue in the Advisory Action mailed December 10, 2002. The new claims are a direct result of the conversation

from the Interview. Applicants have attached a Clean Copy of the Claims to this Amendment for the Examiner's convenience.

Issue Under 35 U.S.C. §103(a)

Claims 1-5 and 7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lobaccaro et al. (J. Med. Chem., 1997, 40, 2217-2227). Applicants assert that patentable distinctions exist between the present invention and Lobaccaro et al.

Distinctions Between the Present Invention and Lobaccaro et al.

Lobaccaro et al. discloses that the 11β position of the steroid in intermediate compounds 5a-b is substituted with ethyl, butyl chains. *See Scheme 1, page 2218.* Scheme 3, page 2219 of Lobaccaro et al. discloses that the 11β position of the steroid has a C10 chain with either TBDMS blocking a terminal hydroxyl group, a hydroxyl or a tosylate.

Lobaccaro et al. fails to disclose a steroid compound of formula I, wherein R^{11} is a hydrocarbon group which may be linear, or branched comprising one singular linear chain having a length of from 5 to 9 carbon atoms as the longest chain. The Examiner asserts that compounds 5a-b in scheme 1 of Lobaccaro et al. render the present invention obvious because the alkyl chains at the 11 position are "substantially similar." The

Examiner has asserted that the results shown in Example III on page 13-15 of the specification fails to show unexpected results; thus, the Examiner asserts that a skilled artisan would find a change from 4 carbons to 5 carbons obvious.

Applicants disagree with the Examiner's assertions. Compounds 5a and 5b in Scheme 1 of Lobaccaro et al have butenyl and vinyl at the 11 position. More importantly, Lobaccaro et al only discloses these compounds as intermediates in a synthetic pathway. In Tables 1 and 2 of Lobaccaro et al, compound 5b is an agonist and to achieve an antagonist Lobaccaro et al have made derivatives with mesylate, tosylate, etc. Lobaccaro et al. only discloses a decyl 11β-alkyl chain with a tosylate; therefore, Lobaccaro fails to have any data to predict longer alkyl chains than 4 carbons. "[I]t appears that the threshold which separates estrogenic from antiestrogenic compounds is rapidly reached when the size of the 11β-alkyl chain increases, with a threshold between C-2 and C-4." *See page 2223, left column, second paragraph.*

After further review of Lobaccaro et al., Applicants assert that Lobaccaro et al. fails to disclose a steroid with an 11β-alkyl chain having ten carbons. Applicants withdraw their statement that "[c]learly, Lobaccaro et al. only discloses hydrocarbon chain lengths of 2, 4 and 10", which was made in the

January 23, 2002 response. *See page 4, top two lines.* Lobaccaro et al. only discloses tosylate, hydroxyl or TBDMS substituted decyl chain. *See Scheme 3.*

Since Lobaccaro et al. only discloses an 11β-alkyl chain without any longer alkyl chains than four carbons, a skilled artisan would not be motivated to make the claimed compounds having 5-9 carbons in chain length. As discussed during the Interview, the identified compounds show unexpected results. Applicants will discuss the unexpected results in greater detail below.

Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Issue Under 35 U.S.C. §103(a)

Claims 1-5 and 7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Napolitano et al. (J. Med. Chem., 1995, 38, 2774-2779). Applicants assert that patentable distinctions exist between the present invention and Napolitano et al.

Distinctions Between the Present Invention and Napolitano et al.

Napolitano et al. discloses that the 11β position of the steroid is substituted or unsubstituted short chain alkyl groups

(less than five carbon atoms). In Table 1, page 2776, Napolitano et al exclusively recites alkyl chains of 2 to 4 carbons in length. However, the Examiner asserts that a skilled artisan would be motivated to extend the carbon chain and expect similar results.

Applicants claim a specific range for the chain length at the 11β position. Applicants believe the unexpected results show that this specific range identifies a series of compounds that have a specific agonist and antagonist profile, which a skilled artisan would not have known. Therefore, any argument of obviousness is overcome because a skilled artisan would not have had a reasonable expectation of success of achieving the selectivity of the present invention. See below for a more detailed explanation of the unexpected results.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Unexpected Results

As discussed during the Interview, in Table A, page 14 of the present specification, Applicants recite that compounds 3, 5, 6, 8 and 11, which are the present invention, are agonist at ER-α and antagonist at ER-β. Compounds 1, 2, 4, 7 and 9-10 are agonist at both ER-α and ER-β. Compounds 1, 2, 4, 7 and 9-10

represent the closest prior art, which is Napolitano et al. Compounds 4 and 5 only differ by one carbon in the side chain at position 11, yet 4 is an agonist ER-β and 5 is an antagonist at ER-β. The same can be said for the difference in compounds 10 and 11.

Applicants have claimed a series of compounds and a series of pharmaceutical compositions that are agonist at ER-α and antagonist at ER-β. The cited prior art provides no motivation to make such compounds or compositions because a skilled artisan would not have had a reasonable expectation of success of making a series of compounds or pharmaceutical compositions that are agonist at ER-α and antagonist at ER-β from reading the cited prior art.

If the Examiner is not persuaded by the data contained in the specification, Applicants can submit additional data in a 37 C.F.R. §1.132 Declaration.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Conclusion

Applicants submit that every issue raised by the Office Action mailed August 27, 2002 has been addressed and rebutted.

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Therefore, the present claims define patentable subject matter and are in condition for allowance.

Attached hereto is a version with markings to show changes made by this amendment.

Should the Examiner believe that an Interview would be helpful in advancing the prosecution of this application, he is invited to telephone Applicants' Attorney at the number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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MWM

Enclosure: Version with Markings to Show Changes Made
Clean Copy of Claims

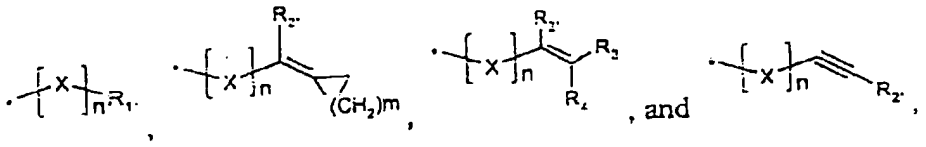
Attorney Docket No. O/98414 US

Version with Markings to Show Changes Made

In the Claims

Please amend the claims as follows:

2. (Twice Amended) A steroid compound according to claim 1, wherein R_{11} is selected from the following group of side-chain structures:

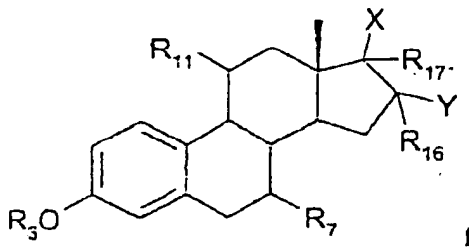


wherein X is CH_2, CH-alkyl or $C(alkyl)_2$, R_1 is H, [aklkyl] alkyl, C_3-C_7 cycloalkyl or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl or C_3-C_7 cycloalkyl, unsubstituted or substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

Claims 8-12 have been added.

Clean Copy of Claims

1. (Amended) A steroid compound satisfying the following structural formula:



formula I

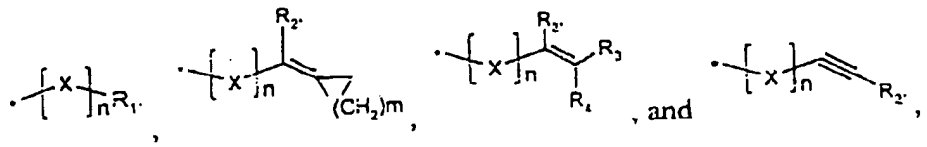
wherein:

one of X and Y is OH, the other being H;

R_3 is H or COR'_3, with R'_3 being alkyl or aryl;

R_7, R_{16}, and R_{17} each independently are H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl; R_{11} is a hydrocarbon group, which may be linear or branched, comprising one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated.

2. (Twice Amended) The steroid compound according to claim 1, wherein R_{11} is selected from the following group of side-chain structures:



wherein X is CH_2, CH-alkyl or $C(alkyl)_2$, R_1 is H, alkyl, C_3-C_7 cycloalkyl or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl or C_3-C_7 cycloalkyl, unsubstituted or substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

3. (Amended) The steroid compound according to claim 1, wherein the longest chain in R_{11} comprises 5-7 carbon atoms.

4. (Amended) The steroid compound according to claim 3, wherein the longest chain in R_{11} comprises 5 carbon atoms.

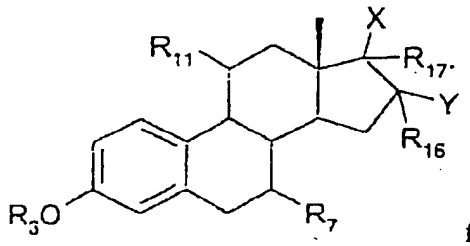
5. (Amended) A pharmaceutical composition comprising a steroid compound according to claim 1 and a pharmaceutically acceptable auxiliary.

7. A method for treating estrogen deficiency disorders, comprising:

administering to a patient afflicted with an estrogen deficiency disorder an effective amount of the pharmaceutical composition of claim 5.

8. A method of inducing ERα agonist activity and ERβ antagonist activity in a patient in need thereof, comprising:

administering an effective amount of a steroid compound satisfying the following structural formula:



formula I

wherein:

one of X and Y is OH, the other being H;

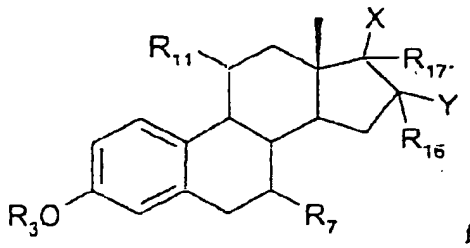
R_3 is H or COR'_3, with R'_3 being alkyl or aryl;

R_7, R_{16}, and R_{17} each independently are H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl;

R_{11} is a hydrocarbon group, which may be linear or branched, comprising one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated.

9. A pharmaceutical composition having ERα agonist activity and having ERβ antagonist activity, comprising:

a steroid compound satisfying the following structural formula:



formula I

wherein:

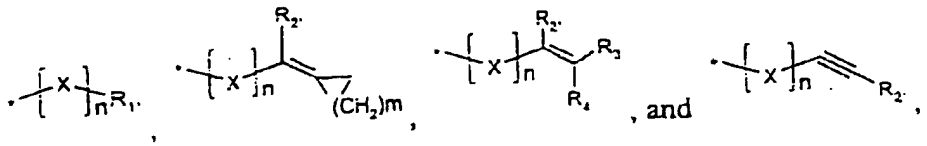
one of X and Y is OH, the other being H;

R_3 is H or COR'_3, with R'_3 being alkyl or aryl;

R_7, R_{16}, and R_{17} each independently are H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl; R_{11} is a hydrocarbon group, which may be linear or branched, comprising one single linear chain having a length of from 5 to 9 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, wherein said chain may be saturated or unsaturated, and

a pharmaceutical acceptable auxiliary.

10. The pharmaceutical composition according to claim 9, wherein R_{11} is selected from the following group of side-chain structures:



wherein X is CH_2, CH-alkyl or $C(alkyl)_2$, R_1 is H, alkyl, C_3-C_7 cycloalkyl or together with X forms a C_3-C_7 ring system, R_2 is H, alkyl or C_3-C_7 cycloalkyl, R_3 and R_4 each independently are H, alkyl or C_3-C_7 cycloalkyl, unsubstituted or substituted with halogen or CN, n is an integer of from 0-9, m is an integer of from 1-5.

11. The pharmaceutical composition according to claim 9, wherein the longest chain in R_{11} comprises 5-7 carbon atoms.

12. The pharmaceutical composition according to claim 11, wherein the longest chain in R_{11} comprises 5 carbon atoms.